UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/297,181	04/26/99	BRACCO L	ST96030-US

005487 HM12/0228
AVENTIS PHARMACEUTICALS, INC.
PATENTS DEPARTMENT
ROUTE 202-206, P.O. BOX 6800
BRIDGEWATER NJ 08807-0800

EXAMINER	
KAUSHAL,S	
ART UNIT	**PAPER NUMBER**
1633	11

DATE MAILED: 02/28/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/297,181	BRACCO ET AL.	
	Examiner	Art Unit	
	Sumesh Kaushal	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-54* is/are pending in the application.

4a) Of the above claim(s) *45,46 and 48-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-44 and 47* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group-I, claims 28-39, 43-44 and 47 in Paper No. 10 is acknowledged. The traversal is on the ground(s) that claims 40-42 depends upon claim 28 of Group-I and relate to the same method as claimed in Group-I. This is found persuasive. Claims 40-42 are included in Group-I and are examined in this office action.

Furthermore the applicant argues that mere fact that words "antibody" and "nucleic acid" method appear in different claims does not mean that distinct inventions exists or that a separate inventive concept is at issue (Paper No:8, 8/18/00, pge 2, para.3). However, this is found unpersuasive because "nucleic acid" and "antibodies (protein)" are structurally and functionally distinct products. The antibodies are biologically active compounds and can be administered directly, whereas expression of any gene product encoded by a nucleic acid requires the delivery of an expression vector (plasmid, virus etc) to the target cells. Therefore, method of using the nucleic acid and antibodies are distinct. The requirement is still deemed proper and is therefore made FINAL.

Claims 45-46 and 48-53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Claims 28-53 are pending. Claims 28-39, 40-44 and 47 are examined in this office action.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 28-39 and 43-44 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of restoring p53 transactivation activity in an **isolated cell** (HT29) containing the p53 mutant (His273) by introducing into the cell a nucleic acid encoding single chain antibody (ScFVs: D3M & 421) which bind to mutated P53 protein, does not reasonably provide enablement for the method as claimed in any and all cells in a host **(in-vivo)** using all viral or non-viral vectors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention **commensurate in scope** with these claims.

4. Claim 47 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, **to make and/or use** the invention..

The claims are drawn to a method of method of restoring p53 transactivation activity in a cell (in-vivo or in-vitro) containing the mutated p53 protein by introducing into the cell a nucleic acid encoding single chain antibody (ScFvs) which bind to mutated P53 protein. The claims are further drawn to the method wherein the ScFvs binds to epitope present in the C-terminal region of p53. The claims are drawn to viral and/or chemical or biochemical vectors wherein the nucleic acid encoding ScFvs is he part of the vector. The claims are further drawn to the method wherein the mutated p53 protein is devoid of tumor-suppressing activity. In addition the claims are drawn to a method of treating hyper-proliferative disorder involving mutated p53 protein by administering to a patient a nucleic acid encoding ScFvs which binds to mutated p53 protein and restore transactivation of the p53 protein.

The specification as filed teaches nucleotide sequences encoding the single chain antibody which binds to p53 (ScFv421, SEQ ID NO:1) or p53 mutant H273 (D3M, SEQ ID NO3), see page 29, example-2. The specification further teaches that single chain antibodies 421 and D3M restores the DNA binding function of the in active mutant Trp248 (page 39, example-6, fig. 6). The specification further teaches the lipofactamine mediated transfection of a

plasmid vector encoding the ScFVs into H1299 tumor cell line, and the expression of the gene product (page 39, example-7, fig.7). In addition the specification teaches the transient transfection of HT29 tumor cell line with plasmid vector encoding D3M and 421 ScFVs (page 39, example-8). The specification further teaches that the D3M and 421 ScFVs are able to increase transcriptional activity of endogenous mutant His273 in HT29 cells in-vitro (page 40 line 18-20, fig-9).

However, i) the specification fails to disclose all single chain antibodies that bind to all p53 mutants and restore the p53 transactivation. ii) The specificaition fails to disclose that besides p53-His273 the D3M and 421 ScFVs are able to restore the transactivation of p53-W248 and p53-G281 mutants. iii) The specification fails to disclose the restoration of p53 transactivation in any cell in-vivo by administering any and all viral or non-viral vectors encoding any ScFVs. iv) In addition, the specification fails to disclose the treatment of any and all hyperproliferative disorders involving any and all p53 mutants by administering a patient a nucleic acid encoding ScFVs which bind to all p53 mutants.

The instant invention encompasses the restoration p53 transactivation in-vivo and/or in vitro by administering a vector encoding a ScFVs which bind to a p53 mutant. Therefore the invention falls in the realm of Cancer Gene Therapy. The Gene therapy is considered highly experimental area of research at this time, and both researchers and the public agree that demonstrable progress to date has fallen short of initial expectations. No cures can as yet be attributed to gene therapy. (Rosenberg et al, Science 287:1751, 2000, Verma, Mol. Ther. 1: 493, 2000, Friedmann, Science 287(5461):2163-5, 2000, Anderson WF, Nature 392:25-30, 1998; Verma et al Nature 389:239-242, 1997, Touchette, Nat. Med. 2(1) 7-8, 1996). None of the human studies to date has shown definite efficacy, despite more than 300 protocols involving 3000 patients since September 1990 (Anderson page 25 col.1 para.1). Most studies have neglected to include well-defined biochemical or clinical end points that would clearly indicate whether the therapy is having a desired effect. The Recombinant DNA Advisory committee (RAC) also emphasized that expectations of current gene therapy protocols have been over sold without any apparent success (Touchette page 7, col.1 para. 2; page 8, col.2 para 1-4). The

advisory panel further emphasized the need for a greater understanding of an underlying mechanism that contributes to a genetic disease along with the pathogenesis of the disease. (Touchette, page 7, col.3, para.3).

Furthermore, it has been difficult to predict the efficiency and out come of transduced therapeutic genes because various factors govern the expression and/or therapeutic potential of transduced genes in vivo. The transduction of target cells represents the first critical step in gene therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vectors (Verma et al, see page 239 col.3 par.2, page 242, table-2). Although the retroviral vectors are the vectors of choice, they require target cells to be in cycling state for the successful delivery of gene of interest. On the other hand vector comprising DNA viruses and liposome coated DNA have been used to transduce non dividing cells but this results in a transient expression due to non-integration of transgenes in host cells (Verma et al page 242, table-2). In addition, the use of adenoviral and adeno associated viral vector is also problematic because these vectors elicits considerable immune response in vivo, which affects the sustained expression of the transduced genes (Verma et al, page 241, col.1, par.3; col.3, par.1). Furthermore, in vitro gene transfer studies are not predictive of in vivo gene therapy because gene transfer frequency is much higher in-vitro models where most of cells are under going rapid cell division, which is quite not the case in vivo environment. In addition, besides the limitations in gene transfer the problem to selectively target cells in vivo is still one of the most difficult obstacle to overcome. The viral particles binds to many cells they encounter in vivo and therefor would be diluted out before reaching their targets (Anderson WF, page 25 col.2, para.4). Although, the gene therapy holds much promise to come the success will only be achieved through continued rigorous research on the most fundamental mechanisms underlying gene delivery and gene expression in animals (Rosenberg, Science 287:1751, 2000).

In addition, the treatment of a cancer is considered highly unpredictable because various genetic and etiological factors govern the development of the cancer. The carcinogenesis is a progressive disorganization and there is a loss of proliferation controls, increased aneusomy and heterogeneity which leaves limited reliable molecular targets for an intervention therapy (Kelloff

et al, Eur. J. Cancer. 35(14):2031-2035, 1999, page 2032, col.2 para.3; page 2034, table-1). Furthermore, the tumors are heterogeneous in respect that they differ in genetic mutations, expression of oncogenes, immunogeneicity and response to environmental changes (Gomez-Navarro et al, Eur. J. Cancer. 35(6);867-885, 1999, page 868, table-1). For example, multiple genetic defects are responsible for the development of breast, lung and colon cancers which renders the cancer gene therapy highly unpredictable (Mastrangelo et al, Semin. in Oncology. 23(1): 4-21, 1996, page 5 col.2, para.3; page 6, table-1; page 8, table-2; page 9 col.1 para. 2; page 19, col.1 para.2). The cancer therapy clearly demands molecular, phenotypic and functional characterization of a particular tumor type that proves amenable to induce cancer amelioration in vivo. Although, mutations in p53 protein reduces sequence-specific DNA-binding activity, more refined molecular characterization have shown that the p53 mutants can be divided into at least three distinct subclasses with respect to tetramerization, conformatinal modulation and intrensic-core domain folding. Therefore, to reactive the function of any p53 mutant in cancer cells a complete understanding of structural and functional properties of all p53 mutants is required (Hupp et al, Biochem. J. 352:1-17, 2000, page 7, col.2, para. 2, fig-3).

At the best the specification as filed only teaches transient transfection of nucleotide sequences encoding the single chain antibody D3M and 421 ScFVs increases the transcriptional activity of p53 mutant His273 in HT29 cells **in-vitro**. Thus, in view of lack of specific guidance in the specification, the skilled artesian at the time of filing would be unable to use the invention as claimed, without an excessive and undue amount of experimentation. The quantity of experimentation required would include making and functional characterization of any and all ScFVs binding to any and all p53 mutants. The experimentation required would further include making any and all viral and/or non-viral encoding the characterized ScFVs. In addition, the experimentation required would also include successful delivery and the expression of nucleotide encoding the ScFVs to elicits the claimed therapeutic effects.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

6. Claims 28-31, 33 and 39 are rejected under 35 U.S.C. 102(a) as being anticipated by Christain et al (Biochem. Biophys. Res. Com. 230:242-246, 1997). The cited art teaches ScFV-421 a single chain antibody that recognizes residues 370-378 of p53 protein (page 242, abstract col.1 para.2). The prior art teaches isolation and cloning of ScFV-421 nucleic acid into pECE vector. The prior art further teaches the transient expression of ScFV-421 in COS-1 cells using lipofecatamin traransfection method (page 243, col.1 para. 2-3). In addition, the prior art teaches that the antibody Pab-421 binds to the C-terminus of P53 protein and restores the transactivation function of a p53 mutant (page 242, col.1 para.2; page 245, col.1, para.1). Thus the cited art anticipated the invention as claimed.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is (703) 305-6838. The examiner can normally be reached on Monday-Friday from 9:00 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Deborah Clark can be reached on (703) 305-4051. The fax-phone number for the organization where this application or proceeding is assigned as (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst

Tracey Johnson, whose telephone number is (703) 308-0377. If the claims are amended canceled and/or added the applicants are advised to follow Amendment Practice under § 1.121 *(http://www.uspto.gov).*

S. Kaushal, AU 1633

Dave
DAVE NGUYEN
AU 1633